Immune correlates and long-term follow-up of a Phase Ia study of MPDL3280A, an engineered PD-L1 antibody, in patients with metastatic renal cell carcinoma (mRCC)

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Disclosures

• Dr. David F. McDermott
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  – Research support from Prometheus Labs
Metastatic Renal Cell Carcinoma (mRCC)

- The median OS for treatment-naive patients with mRCC is approximately 2 years\(^1,2\)
- VEGF TKIs are the standard of care for clear cell mRCC but are associated with chronic toxicity (e.g., fatigue, diarrhea, HFS, etc.) and acquired resistance\(^3\)
- A high unmet need exists for agents that induce a high proportion of durable tumor responses with acceptable toxicity for patients with mRCC\(^3\)


McDermott et al., 26-30 September 2014, Madrid, Spain
MPDL3280A is an Engineered Anti-PD-L1 Antibody That Inhibits the Binding of PD-L1 to PD-1 and B7.1

- Inhibiting PD-L1/PD-1 and PD-L1/B7.1 interactions can restore antitumor T-cell activity and enhance T-cell priming

- MPDL3280A leaves the PD-L2/PD-1 interaction intact, maintaining immune homeostasis and potentially preventing autoimmunity

MPDL3280A Phase Ia

Phase Ia Expansion Ongoing

<table>
<thead>
<tr>
<th>RCC</th>
<th>NSCLC</th>
<th>Melanoma</th>
<th>Bladder</th>
<th>Other Tumor Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. All-comers</td>
<td>1. All-comers</td>
<td>All-comers</td>
<td>1. PD-L1+ patients</td>
<td>1. PD-L1+ patients</td>
</tr>
<tr>
<td>2. PD-L1+ patients</td>
<td>2. PD-L1+ patients</td>
<td></td>
<td>2. All-comers</td>
<td>2. All-comers</td>
</tr>
</tbody>
</table>

MPDL3280A administered by IV q3w for up to 16 cycles

**Key Eligibility Criteria**

*Measurable disease per RECIST v1.1*

*ECOG PS 0 or 1*

- First RCC patient was enrolled on Dec 12, 2011. Last RCC patient was enrolled on Jul 18, 2013
MPDL3280A: mRCC Baseline Characteristics

*Safety-evaluable population with RCC in Phase I expansion*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients, N = 69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>61 (33-81)</td>
</tr>
<tr>
<td>Male</td>
<td>77%</td>
</tr>
<tr>
<td>ECOG PS 0 / 1</td>
<td>54% / 46%</td>
</tr>
<tr>
<td>Histologic subtypes, n (%)</td>
<td></td>
</tr>
<tr>
<td>Clear cell</td>
<td>62 (90%)</td>
</tr>
<tr>
<td>Non–clear cell</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Fuhrman grade 4 or with sarcomatoid histology</td>
<td>20 (29%)</td>
</tr>
<tr>
<td>MSKCC poor risk, n (%)</td>
<td>18 (26%)</td>
</tr>
<tr>
<td>Prior nephrectomy, n (%)</td>
<td>66 (96%)</td>
</tr>
<tr>
<td>Previous systemic therapies, n (%)</td>
<td>60 (87%)</td>
</tr>
<tr>
<td>Cytokine-based</td>
<td>27 (39%)</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitor</td>
<td>40 (58%)</td>
</tr>
<tr>
<td>mTOR inhibitor</td>
<td>17 (25%)</td>
</tr>
<tr>
<td>Lung/liver/bone/brain metastases at enrollment, n (%)</td>
<td>49 (71%) / 16 (23%) / 24 (35%) / 3 (4%)</td>
</tr>
</tbody>
</table>

Clinical data cutoff Apr 21, 2014; MSKCC, Memorial Sloan Kettering Cancer Center.

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MPDL3280A: Treatment-Related Adverse Events

Safety-evaluable population with RCC in Phase I expansion

- Median duration of treatment was 239 days (range, 21-834 days)
- 80% of patients experienced a treatment-related AE
- Treatment-related Grade 3 AEs occurred in 11 patients (16%), including anemia (4%), dehydration (3%), fatigue (3%) and hypophosphatemia (3%)
- No treatment-related Grade 4 AEs or deaths were reported

<table>
<thead>
<tr>
<th>Patients With RCC, N = 69 (Data cutoff Apr 21, 2014)</th>
<th>All Grade(^a) n (%)</th>
<th>Grade 3-4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>15 (22%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>11 (16%)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10 (15%)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>10 (15%)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>7 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (10%)</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) Includes all-grade events occurring in ≥ 7 patients (10%).
MPDL3280A: Efficacy by PD-L1 IHC (IC)

*Efficacy-evaluable population with clear cell RCC*

<table>
<thead>
<tr>
<th>PD-L1 IHC - tumor-infiltrating immune cells (IC)(^a), n = 62</th>
<th>ORR (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>15% (8-25)</td>
</tr>
<tr>
<td>IHC (IC) 1/2/3</td>
<td>20% (9-37)</td>
</tr>
<tr>
<td>IHC (IC) 0</td>
<td>10% (2-30)</td>
</tr>
</tbody>
</table>

- 24-week PFS rate was 51% (95% CI: 38-63)
- 1 CR (IHC [IC] 3)
- ORR for Fuhrman grade 4 or sarcomatoid clear cell RCC (n = 18) was 22% (95% CI: 8, 47)

\(^a\) A PD-L1+ cohort of patients was enrolled. 6 patients had unknown PD-L1 IHC (IC) status.

Investigator-assessed confirmed ORRs per RECIST v1.1.


IHC 3: ≥ 10% of ICs are PD-L1+; IHC 2: ≥ 5% but < 10% of ICs are PD-L1+; IHC 1: ≥ 1% but < 5% of ICs are PD-L1+; IHC 0: < 1% are PD-L1+.
MPDL3280A: Summary of ORR in Clear Cell RCC

Efficacy-evaluable population with clear cell RCC in Phase I expansion

- Median duration of follow-up was 9 months (range, 1-27 months)

CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; UE, unable to evaluate.

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MPDL3280A: Efficacy by MSKCC Prognostic Group

**Efficacy-evaluable population with clear cell RCC**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>All patients</th>
<th>IHC (IC) 1/2/3&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>ORR, n (%)</td>
</tr>
<tr>
<td>Overall</td>
<td>62</td>
<td>9 (15%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 CR and 8 PRs</td>
</tr>
<tr>
<td>Favorable</td>
<td>10</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>36</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Poor</td>
<td>15</td>
<td>4 (27%)</td>
</tr>
</tbody>
</table>

- Higher response rate observed in MSKCC poor-risk patients with PD-L1 IHC (IC) 1/2/3 expression

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<sup>a</sup> 1 patient had unknown PD-L1 IHC (IC) status.

MSKCC, Memorial Sloan Kettering Cancer Center.


IHC 3: ≥ 10% of ICs are PD-L1+; IHC 2: ≥ 5% but < 10% of ICs are PD-L1+; IHC 1: ≥ 1 % but < 5% of ICs are PD-L1+; IHC 0: < 1% of ICs are PD-L1+.

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MPDL3280A: Response in Patient With Sarcomatoid Variant mRCC

- 51-year-old man with metastatic RCC (75% sarcomatoid variant) diagnosed Oct 2011 with T3aN2 disease, s/p L nephrectomy; now metastatic to lungs, skin and bone
  - Prior sunitinib, temsirolimus and XRT to T9
- Poor MSKCC risk and ECOG PS 1
- PD-L1 IHC (IC) positive (IHC 3)
- Duration of response was 76 weeks
MPDL3280A: irRC Partial Response in Patient With Metastatic Oncocytic Papillary RCC

- 72-year-old woman with metastatic RCC oncocytic papillary RCC s/p R nephrectomy and sunitinib
- PD-L1 IHC (IC) negative (IHC 0)

irRC, immune-related response criteria.
Yale School of Medicine (Sznol/Herbst).
McDermott et al., 26-30 September 2014, Madrid, Spain
Rationale to Combine MPDL3280A With Bevacizumab

- Single agent bevacizumab (10 mg/kg) has demonstrated a 10% ORR [95% CI: 2.9, 24.2] in RCC\(^1\)

- Anti-VEGF therapy has immunomodulatory properties
  - Increases trafficking of T cells into tumors\(^2,3\)
  - Reduces suppressive cytokines and infiltrating Tregs and MDSCs\(^4,5\)

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MDSC, myeloid-derived suppressor cell; Tregs, regulatory T cells.


McDermott et al., 26-30 September 2014, Madrid, Spain
MPDL3280A + Bevacizumab: Phase Ib Study Design Arm A

- Primary objectives: safety, tolerability, DLT and MTD
- Secondary objectives: preliminary anti-tumor activity and PK

\[ \text{Arm A} \]

\[ \text{Solid tumors} \]

MPDL3280A IV q3w + Bev 15 mg/kg IV q3w

\[ \text{Solid tumors} \]

Biopsy

CRC

Safety

Biopsy

RCC

n = 10

\[ \text{Dose escalation} \]

\[ \text{Dose expansion} \]

\[ \text{Lieu et al., abstract 1049O, presented Saturday.} \]

\[ \text{McDermott et al., 26-30 September 2014, Madrid, Spain} \]
MPDL3280A + Bevacizumab: Summary of Phase Ib Results

Safety and efficacy of patients in Arm A

• Safety
  – All patients in Arm A (n = 35) experienced an AE, with 49% experiencing a G3-4 AE, regardless of attribution
  – 1 MPDL3280A-related Grade 3 AE occurred (1 case of neutropenia in Arm A)
  – No Grade 4 AEs or deaths were attributed to MPDL3280A

• Efficacy in patients with 1L clear cell RCC
  – 4 of 10 patients demonstrated an objective response
  – 5 of 10 patients experienced stable disease
  – Responding patients included 2 with IHC (IC) 1, 1 with IHC (IC) 0 and 1 with IHC (IC) unknown

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Lieu et al., abstract 1049O, presented Saturday.
IHC 3: ≥ 10% of ICs are PD-L1+; IHC 2: ≥ 5% and < 10% of ICs are PD-L1+. IHC 1: ≥ 1% and < 5% of ICs are PD-L1+; IHC 0: < 1% ICs are PD-L1+.

McDermott et al., 26-30 September 2014, Madrid, Spain
MPDL3280A + Bevacizumab: Duration of Treatment and Response in 1L RCC

**Efficacy-evaluable population with 1L clear cell RCC in Arm A**

- SD $\geq$ 24 weeks in 4 patients
- 9 of 10 patients with mRCC remain on study treatment

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**PD-L1 IHC (IC)**

- 1
- 0
- 0
- 0
- 1
- 0
- 0
- Missing
- 1
- 1
- 3

**Time on study (weeks)**

- 0
- 3
- 6
- 9
- 12
- 15
- 18
- 21
- 24
- 27
- 30
- 33
- 36
- 39
- 42

- On-study
- No PD/Death
- First PR/CR
- First PD

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* Liew et al., abstract 1049O, presented Saturday.

Patients dosed by Apr 7, 2014 who had at least 1 scan; data cutoff Jul 7, 2014.

**IHC 3:** ≥ 10% of ICs are PD-L1+; **IHC 2:** ≥ 5% and < 10% of ICs are PD-L1+. **IHC 1:** ≥ 1% and < 5% of ICs are PD-L1+; **IHC 0:** < 1% ICs are PD-L1+.
Study WO29074 MPDL3280A: Phase II Trial in mRCC (NCT01984242)

Previously untreated mRCC
N = 300

Randomized

MPDL3280A (IV)
1200 mg q3w × 8 cycles or up to 1 y (6-wk cycles)

MPDL3280A (IV)\textsuperscript{a} + bevacizumab (IV)\textsuperscript{b}
\textsuperscript{a} 1200 mg q3w × 8 cycles or up to 1 y (6-wk cycles)
\textsuperscript{b} 15 mg/kg q3w until PD (6-wk cycles)

Sunitinib (oral)
50 mg/day for 4 wk, 2 wk rest, until PD (6-wk cycles)

• Key objectives: evaluate efficacy of sunitinib vs MPDL3280A as monotherapy or in combination with bevacizumab
• Primary endpoint: PFS per RECIST v1.1
• Crossover allowed
MPDL3280A: Conclusions

• MPDL3280A was well tolerated
  – Both as a single agent and in combination with bevacizumab
• MPDL3280A demonstrated promising efficacy in previously treated clear cell mRCC
  – Median PFS = 24 weeks (range, 5-98+ weeks)
  – ORR = 22% for Fuhrman grade 4 or sarcomatoid clear cell mRCC
• Preliminary data indicated that MPDL3280A had better efficacy in patients with PD-L1 expressed on tumor-infiltrating immune cells
• MPDL3280A demonstrated clinical activity in combination with bevacizumab in 1L clear cell mRCC
  – ORR = 40%; SD = 50%
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Centre Léon-Bérard (Cassier)
Comprehensive Cancer Centers of Nevada (Braiteh)
Dana-Farber Cancer Institute (Hodi)
Gustave Roussy (Bahleda, Hollebecque)
Johns Hopkins (Drake, Emens)

Massachusetts General Hospital (Lawrence, Lee)
Moffitt Cancer Center (Antonia, Zhang)
New York Oncology Hematology (Garbo)
Sarah-Cannon Research Institute (Burris)
Stanford University (Kohrt, Srinivas)
Vall d’Hebron University Hospital (Tabernero)
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